Repurposed drug may offer diagnosis, treatment for traumatic nerve damage

November 14 2016

Researchers at the University of Rochester Medical Center believe they have identified a new means of enhancing the body's ability to repair its own cells, which they hope will lead to better diagnosis and treatment of traumatic nerve injuries, like those sustained in car accidents, sports injuries, or in combat. In a study published today, the team showed that a drug previously approved for other purposes can 'wake up' damaged peripheral nerves and speed repair and functional recovery after injury.

The study appearing in *EMBO Molecular Medicine*, demonstrates for the first time that 4-aminopyridine (4AP), a drug currently used to treat patients with the chronic nerve disease, multiple sclerosis, has the unexpected property of promoting recovery from acute nerve damage. Although this drug has been studied for over 30 years for its ability to treat chronic diseases, this is the first demonstration of 4AP's benefit in treating acute nerve injury and the first time those benefits were shown to persist after treatment was stopped.

Study authors, John Elfar, M.D., associate professor of Orthopaedics, and Mark Noble, Ph.D., Martha M. Freeman, M.D., Professor in Biomedical Genetics, and their laboratory team, found that daily treatment with 4AP promotes repair of myelin, the insulating material that normally surrounds nerve fibers. When this insulation is damaged, as occurs in traumatic peripheral nerve injury, nerve cell function is impaired. These researchers found that 4AP treatment accelerates repair of myelin damage and improvement in nerve function.

These findings advance an area of research that has been stagnant for nearly 30 years and may address unmet needs of traumatically injured patients in the future. The current standard of care for traumatic peripheral nerve injury is "watchful waiting" to determine whether a nerve has the ability to spontaneously recover, or if it will require surgery.

The problem, says Elfar, a Sports Medicine surgeon specializing in hand, wrist, elbow and shoulder repairs, is that "the patient who may recover is recovering so slowly that nerve-dependent tissues are in jeopardy, and the patient who needs surgery has to wait for weeks for the diagnosis that surgery is appropriate. That delay means that surgery is less effective."

Elfar's and Noble's team, which includes Kuang-Ching Tseng, Ph.D., former graduate student in the Center for Musculoskeletal Research at the University of Rochester Medical Center and first author of the study, also found that treating mice with a single dose of 4AP one day after nerve crush injury improved muscle function within an hour. In this model, nerves are damaged, but not completely severed. The team believes this finding may suggest that 4AP could be used immediately after an injury to diagnose whether a nerve is severed, however further studies are required to determine if this will work in humans.

If their results can be translated into humans, it could mean earlier and more rapid diagnosis of traumatic peripheral nerve injuries, enabling earlier surgery and better outcomes for patients whose nerves have been completely severed. For patients whose nerves are still connected, 4AP treatment could offer a new means to speed recovery, where none has previously existed.

The Department of Defense has recognized the potential impact this could have for soldiers in combat situations and granted $1 million to

Elfar and Noble to continue this research over the next three years.

"This is an ideal outcome for development of a treatment to promote tissue regeneration," said Noble. "The drug we use to identify injuries that need repair of their insulating myelin is the same drug we use to promote the needed repair. As 4AP has been well-studied in chronic injuries, and is approved for treating multiple sclerosis, the new benefits we discovered can be explored rapidly and much more cheaply than is needed for developing an entirely new drug."

Beyond nerve injuries sustained during accidents or in the line of duty, the researchers are also looking into using 4AP to repair nerve conduction after routine surgeries. Removal of the prostate, for example, can cause nerve damage that leaves patients with incontinence and erectile dysfunction, the burden and stigma of which may contribute to prostate cancer patients refusing the surgery.

Elfar and Noble hope to begin a clinical trial to test this in the near future. The proposed trial has been approved by the Food and Drug Administration (FDA), and University of Rochester researchers and clinicians are completing the planning stages before recruiting participants.

More information: *EMBO Molecular Medicine*, embomolmed.embopress.org/cgi/d … 15252/emmm.201506035

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